8-SUBSTITUTION DERIVATIVES OF D-6-METHYLERGOLINE-I*

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Received August 14th, 1981

Reactions of esters *I* and *II* with methylsulphinylmethylsodium in dimethyl sulphoxide afforded β-keto sulphoxides *III* and *IV*, which were converted either into compounds *V* and *VI* under the conditions of the Pummerer rearrangement, or into ketones *VII* and *VIII* by the action of aluminium amalgam in 1,2-dimethoxyethane. Reduction of the compounds *III* and *V* with sodium borohydride produced β-hydroxy sulphoxide *IX* and dihydroxy derivative *X* respectively; the latter was characterised in the form of derivatives *XI* and *XII*. Condensation of the compound *III* with 1,2-diaminobenzene in acetic acid gave quinoxaline derivative *XIII*. The compounds prepared had no marked antilactation or antinidation activity.

The diversity in pharmacological action of semi-synthetic derivatives of ergoline has motivated syntheses of series of compounds tested for specific biological activities. The nature and configuration of the substituents at position 8 of the ergoline skeleton (the centre of chirality) proved to have a marked effect on the physiological activity of the compounds (see reviews[1,2]). The present communication describes syntheses of ergoline derivatives having substituents bound equatorially to the 8-position, with a view to preparing compounds of the β-keto sulphoxide type and products of their chemical transformation (Table I).

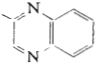
The starting compounds for the syntheses were methyl ester of D-dihydrolysergic-I acid[3] (*I*), and D-6-methyl-8-ergoline-I-ylacetic acid[4] (*II*). The ready accessibility of the carbanion carrying the methylsulphinyl group and its well-known high reactivity with esters of aliphatic and aromatic acids[5-7] were made use of for reactions with the esters *I* and *II*. Methylsulphinylmethylsodium was obtained as described by Corey and Chaykovsky[8] by the action of sodium hydride on dimethyl sulphoxide at an elevated temperature. The reactions with compounds *I* and *II*, giving rise to compounds *III* and *IV* respectively, were conducted in dimethyl sulphoxide or its mixture with dimethoxyethane. The compound *IV* was obtained in poor yields and an oily form, with an admixture of accompanying substances, probably as a result of the possible reaction of the nucleophilic agent with the hydrogen atoms of the methylene group adjacent to the ester function. In the acid medium of acetic acid the β-keto sulphoxide *III* undergoes the Pummerer rearrangement[5,9,10] to the acetyl derivative *V*, arising as a mixture of diastereoisomers, due to the formation of a new chirality centre. Compound *IV* analogously rearranged to compound *VI*.

* Part LXVII in the series Ergotic Alkaloids; Part LXVI: This Journal *47*, 3432 (1982).

Collection Czechoslovak Chem. Commun. [Vol. 48] [1983]

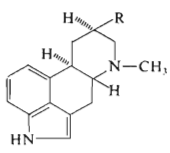
TABLE I

8-Substitution derivatives of D-6-methylergoline-I

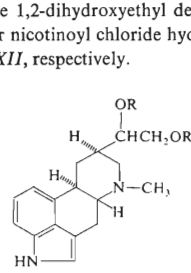
Compound	R	Formula (mol.mass)	M.p., °C (solvent)	$[\alpha]_{20}^{D}$ (*c*)	Calculated/Found			
					% C	% H	% N	% S
III	$COCH_2SOCH_3$	$C_{18}H_{22}N_2O_2S$ (330·5)	140—142 (benzene)	−114·8° (0·5)	65·42 65·08	6·71 6·83	8·47 8·20	9·70 9·77
V	$COCH(SCH_3)(OCOCH_3)$	$C_{20}H_{24}N_2O_3S$ (372·5)	197—199 (methanol)	−99·2° (0·5)	64·49 64·29	6·49 6·65	7·52 7·36	8·60 8·48
VI	$CH_2COCH(SCH_3)(OCOCH_3)$	$C_{21}H_{26}N_2O_3S$ (386·5)	173—175 (methanol)	−99·1° (0·38)	65·26 65·05	6·78 6·72	7·24 7·00	8·29 8·39
VIII	CH_2COCH_3	$C_{18}H_{22}N_2O$ (282·4)	201—202 (methanol)	−95·3° (0·4)	76·56 76·57	7·85 8·09	9·94 9·74	— —
IX	$CH(OH)CH_2SOCH_3$	$C_{18}H_{24}N_2O_2S$ (332·5)	232—234 (ethanol)	−101·4° (0·35)	65·02 65·43	7·28 7·30	8·43 8·33	9·64 9·43
X	H	$C_{17}H_{22}N_2O_2$ (286·4)	240—242 (ethanol)	−112·5° (0·34)	71·30 71·28	7·74 7·81	9·78 9·60	— —
XI	$COCH_3$	$C_{21}H_{25}N_2O_4$ (369·4)	170—171 (benzene)	−89·0° (0·19)	68·27 68·47	6·82 6·98	7·58 7·41	— —
XII		$C_{29}H_{28}N_4O_4$ (496·6)	205—207 (benzene)	−64·0° (0·28)	70·14 70·15	5·68 5·82	11·28 11·23	— —
XIII		$C_{23}H_{22}N_4$ (354·4)	230—232 (chloroform-methanol)	−108·2° (0·25)	77·93 77·62	6·26 6·30	15·81 15·64	— —

Since the methylsulphinyl group in β-keto sulphoxides can easily be replaced by a hydrogen atom, with the formation of ketones[8,10], we reduced compounds *III* and *IV*, with aluminium amalgam in aqueous 1,2-dimethoxyethane, to D-6-methyl--8-acetylergoline-I (*VII*) (ref.[11]) and D-6-methyl-8-acetonylergoline (*VIII*), respectively. The preparation of compound *VII*, starting from compound *I*, *via* compound *III*, represents a new approach to the synthesis of this compound, essentially different from the previous methods[11–13].

Reduction of compound *III* with an excess of sodium borohydride in methanol gave rise to β-hydroxy sulphoxide *IX*. The action of the same reducing medium on compound *V*, in analogy to ref.[10], brought about reduction of the keto group with the simultaneous splitting-off of the sulphide and hydrolysis of the geminal acetoxy group, which led to the formation of the 1,2-dihydroxyethyl derivative *X*. Acylation of *X* by means of acetyl chloride and/or nicotinoyl chloride hydrochloride in pyridine afforded the diacyl derivatives *XI* and *XII*, respectively.



I–IX, XIII



X–XII

R, for compounds *I*: $COOCH_3$; *II*: CH_2COOCH_3; *IV*: $CH_2COCH_2SOCH_3$; *VII*: $COCH_3$; R, for compounds *III*, *V*, *VI*, *VIII–XIII* see table I.

β-Keto sulphoxides can be regarded as certain analogues of 1,2-diketones, and, with suitable substituents, can be easily cyclized in the presence of an acid catalyst to heterocyclic compounds[9]. Similarly, their condensation with 1,2-diamino compounds in neutral[14] or acid[15,16] media results in derivatives of pyrazine[14], quinoxaline[14,16] or pteridine[15]. In our experiments, adhering to the described procedure[15], compound *III* was condensed with 1,2-diaminobenzene in the medium of acetic acid with anhydrous sodium acetate and the quinoxaline derivative *XIII* was isolated. The formation of this derivative is in accordance with the conceptions published[15].

The structures of selected compounds were confirmed by IR and ^{1}H NMR spectra. The presence of a carbonyl group in compounds containing a ketone grouping followed from the IR spectra by the presence of a band at 1 690–1 700 cm^{-1}.

In informative screening tests the compounds prepared showed no significant pharmacological effects. In accordance with the published data[11], compound *VII* exhibited moderate antinidation and antilactation effects.

EXPERIMENTAL

The melting points, determined on the Kofler block, are not corrected. The analytical samples were dried at temperatures adequate to their melting points and a pressure of 70 Pa. Purity of the compounds prepared was checked by TLC on reflex foils Silufol UV_{254} (Kavalier) in a system chloroform–ethanol–triethylamine (92 : 6 : 2), the spots were detected under ultraviolet light (254 and 366 nm) and by spraying the foils with a 0·5% solution of *p*-dimethylaminobenzaldehyde in cyclohexane, followed by their exposure to vapour of hydrogen chloride. The specific rotations of the compounds, free of the crystallization solvents, were measured with a polarimeter Perkin–Elmer 141 in pyridine. The ^{1}H NMR spectra were measured, employing a spectrometer Tesla BS 487 C (80 MHz), in deuteriochloroform or hexadeuteriodimethyl sulphoxide with the use of tetramethylsilane as internal standard. The IR spectra were measured by the KBr technique with a spectrometer Infrascan (Hilger). The reaction mixtures were chromatographed on columns of silica gel Kieselgel 60 (Merck), mesh size 70–230. The dimethyl sulphoxide used for the preparative of methylsulphinylmethylsodium had been dried with molecular sieves Potassit A 5 for 48 h and, just prior to use, by distillation from calcium hydride.

Reactions of Methylsulphinylmethylsodium with Methyl Esters *I* and *II*

A suspension of sodium hydride (2·4 g, 0·1 mol) in dimethyl sulphoxide (32 ml) under nitrogen was heated to 70–75°C for 1 h. The solution was then cooled to 20°C, a solution of ester *I* (2·27 g, 0·008 mol) or *II* (2·38 g, 0·008 mol) in 5 ml of dimethyl sulphoxide was added dropwise under stirring, which was continued for 1 h at 20°C. After decomposition of the mixture with 8 ml of water under cooling to 20°C the dimethyl sulphoxide was distilled off and the residue was dissolved in 150 ml of water. The solution was brought to pH 5 with dilute (1 : 1) hydrochloric acid, then to pH 7 with a saturated solution of sodium carbonate. The resinous products (especially after the reaction with ester *II*) were filtered off and the filtrate was extracted with three 30 ml portions of chloroform with 2% of ethanol. The chloroform portions were combined, dried with anhydrous sodium sulphate, filtered and distilled. Crystallization of compound *III* from benzene gave 2·3 g (87%) of the pure substance. ^{1}H NMR spectrum (hexadeuterodimethyl sulphoxide) δ 10·60 (bs, 1 H, NH), 6·60–7·20 (m, 4 H, ArH), 4·20 (m, 2 H, $COCH_2SO$), 2·62 (s, 3 H, $SOCH_3$), 2·35 (s, 3 H, NCH_3). IR spectrum: 3 400 (NH), 1 690 (C=O, ketone), 1 600 (Ar), 1 030 (S=O), 750 cm^{-1} (1,2,3-trisubstituted Ar). The crude compound *IV*, containing four accompanying compounds, was purified by column chromatography, chloroform with 3% of ethanol being used as eluant. The oily fraction thus obtained (0·8 g, 29%) was used for further reactions (content of admixtures *c.* 5%).

Rearrangement of Compounds *III* and *IV*

A solution of compound *III* (15·6 g, 0·047 mol) in 300 ml of glacial acetic acid under nitrogen was refluxed for 2 h. After cooling the acetic acid was distilled off; the residue was stirred up in 500 ml of water and the solution was brought to *c.* pH 8 with solid sodium carbonate. The precipitate was washed with water, dried and purified by column chromatography, benzene with 5% of ethanol being used as eluant. The head fractions were combined, taken to dryness and crystallized from methanol; yield 10·55 g (60·3%) of compound *V* as a mixture of diastereoisomers. ^{1}H NMR spectrum (deuteriochloroform): δ 8·15 (bs, 1 H, NH), 6·70–7·30 (m, 4 H, Ar—H), 5·30, 5·25 (s, $\sum$ 1 H, COCH), 2·48 (s, 3 H, N—CH_3), 2·32 (s, 3 H, SCH_3), 2·18, 2·17 (s, $\sum$ 3 H, $COCH_3$). IR spectrum: 3 400 (NH), 1 740 (acetyl), 1 690 (C=O, ketone), 1 600 (Ar), 750 cm^{-1} (1,2,3-trisubstituted Ar). Mass spectrum: *m/e* 372 (M^+, $C_{20}H_{24}N_2O_3S$). Compound *VI* was prepared analogously from 0·2 g of compound *IV* in 5 ml of acetic acid; yield 35 mg (16%).

Reduction of Compounds *III* and *IV* with Aluminium Amalgam

To 0·008 mol of compound *III* (2·64 g) or *IV* (2·75 g) dissolved in a mixture of 1,2-dimethoxyethane (200 ml) and water (60 ml) was gradually added, under cooling to 0°C, 6·48 g (0·24 mol) of an aluminium foil (strips 1 × 5 cm), pre-activated by dipping in a 10% solution of mercuric chloride and rinsed with ethanol and ether. After the last portion of activated aluminium was added, the mixture was stirred for 30 min at 0°C, then heated for 1 h to 50–60°C, cooled down, diluted with 150 ml of chloroform and filtered. The filtrate was extracted with two 200 ml portions of water, dried with anhydrous sodium sulphate and purified by column chromatography with chloroform as eluant. Yield after crystallization 0·9 g (42%) of compound *VII*, m.p. 208 to 210°C (methanol). $[\alpha]_{20}^{D} = -88°$, $c = 0·3$ (*cf.* ref.[11]), or 0·73 g (32%) of compound *VIII*. *VIII*: ^{1}H NMR spectrum (hexadeuteriodimethyl sulphoxide): δ 10·48 (bs, 1 H, NH), 6·60–7·20 (m, 4 H, Ar–H), 2·31 (s, 3 H, NCH_3), 2·12 (s, 3 H, $COCH_3$). IR spectrum: 3 400 (NH), 1 700 (C=O, ketone), 1 600 (Ar), 750 cm^{-1} (1,2,3-trisubstituted Ar).

D-6-Methyl-8-(1-hydroxy-2-methylsulphinylethyl)ergoline-I (*IX*)

To a solution of compound *III* (1·0 g, 0·003 mol) in 50 ml of methanol was added in six portions a total of 3·0 g (0·078 mol) sodium borohydride at room temperature. The mixture was boiled under a reflux condenser for 2 h, cooled down and decomposed with 200 ml of water. The organic part was taken into two 50 ml portins of chloroform. The crude product obtained after concentration was crystallized from ethanol. Yield 0·5 g (45%) of compound *IX*. ^{1}H NMR spectrum (hexadeuteriodimethyl sulphoxide): δ 10·60 (bs, 1 H, NH), 6·70–7·20 (m, 4 H, ArH), 5·02 (bs, 1 H, OH), 3·80 (bm, 1 H, CH), 3·60 (s, 3 H, $SOCH_3$), 2·30 (s, 3 H, NCH_3).

D-6-Methyl-8-(1,2-dihydroxyethyl)ergoline-I (*X*)

To a solution of mercaptol *V* (9·3 g, 0·025 mol) in 460 ml of methanol was added in portions, in the course of 4 h, a total of 38 g (1·0 mol) of sodium borohydride; the mixture was stirred at room temperature for 6 h and left standing overnight. After decomposition with water (500 ml) and repeated extraction with chloroform (2 × 100 and 3 × 50 ml), the combined portions were dried with anhydrous magnesium sulphate and concentrated. The crude product was dissolved in a mixture of chloroform with 5% of ethanol and purified by column chromatography. After removal of the less polar impurities in the first fractions and the following elution of the column with a system chloroform–ethanol 1 : 1 (v/v) and finally ethanol, the corresponding fractions were combined and crystallized. Yield 4·8 g (67%) of compound *X*. IR spectrum: 3 380 (OH, NH), 1 600 (Ar), 750 cm^{-1} (1,2,3-trisubstituted Ar).

Acylation of D-6-Methyl-8-(1,2-dihydroxyethyl)ergoline-I

To a solution of compound *X* (0·86 g, 0·003 mol) in 30 ml of pyridine, cooled down to 10°C, was added dropwise 0·01 mol of acetyl chloride (0·78 g) or nicotinoyl chloride hydrochloride (1·78 g). The mixture was either stirred for 4 h at room temperature (preparation of compound *XI*) or refluxed for 6 h (preparation of compound *XII*). In the latter case, another 1·78 g of nicotinoyl chloride hydrochloride was then added and the mixture was kept boiling for 8 more h. After concentration of the mixture, stirring up the residue in 200 ml of water and alkalinization with concentrated ammonium hydroxide to pH 8, the organic portion was taken into a mixture of chloroform with 10% of ethanol (3 × 50 ml), dried with anhydrous sodium sulphate and concentrated. The crude product was purified by column chromatography, the eluant being chloro-

form (compound *XI*) or benzene with 3% of methanol (compound *XII*). The corresponding fractions were combined and crystallized. Yields 0·6 g (54%) of compound *XI* and 1·0 g (67%) of compound *XII*.

XI: ^{1}H NMR spectrum (deuteriochloroform): δ 8·25 (bs, 1 H, NH), 6·70—7·20 (m, 4 H, ArH), 5·00 (bm, 1 H, CH), 4·30 (m, 2 H, OCH_2), 2·40 (s, 3 H, NCH_3), 2·05 (s, 3 H, $COCH_3$), 2·03 (s, 3 H, $COCH_3$). IR spectrum: 3 400 (NH), 1 720 (C=O, ester), 1 603 (Ar), 750 cm^{-1} (1,2,3-trisubstituted Ar).

XII: ^{1}H NMR spectrum (deuteriochloroform): δ 9·18 (m, 2 H, N=CH), 8·75 (m, 2 H, N=CH—C—O), 8·30 (bs, 1 H, NH), 8·20 (m, 2 H, $C_{(3)}$—H pyridine), 6·80—7·50 (m, 6 H, Ar—H), 5·50 (bm, 1 H, OCH), 4·70 (m, 2 H, OCH_2), 2·50 (s, 3 H, NCH_3). IR spectrum: 3 380 (NH), 1 712 (C=O, ester), 1 580 (Ar), 750 cm^{-1} (1,2,3-trisubstituted Ar).

D-6-Methyl-8-(2-quinoxalinyl)ergoline-I (*XIII*)

To a solution of compound *III* (3·3 g, 0·01 mol) in 100 ml of acetic acid was added, at room temperature, 1·1 g (0·01 mol) of 1,2-diaminobenzene and 2·7 g (0·02 mol) of anhydrous sodium acetate. The mixture was boiled under a reflux condenser for 4 h and left standing overnight at room temperature. The acetic acid was distilled off in a vacuum evaporator and the residue was dissolved in 100 ml of water. The solution was brought to pH 7·5 with aqueous ammonia. The precipitate was collected on a filter, washed with water and dried. The crude product was purified by column chromatography, chloroform being employed as eluant. The corresponding fractions were combined and crystallized; yield 2·6 g (76%) of compound *XIII*. ^{1}H NMR spectrum (hexadeuteriodimethyl sulphoxide): δ 9·90 (bs, 1 H, NH), 9·10 (s, 1 H, N=CH), 7·70—8·20 (m, 4 H, ArH), 6·70—7·30 (m, 4 H, ArH(indol)), 2·46 (s, 3 H, NCH_3).

The elemental analyses were performed by Mrs J. Komancová (Analytical Department, head Dr J. Körbl), the polarimetric measurements by Mrs M. Bezděková (Physico-chemical Department, head Dr B. Kakáč). The preliminary pharmacological assessment of the prolactin-inhibition effects was carried out by Dr K. Řežábek and coworkers (Pharmacological Department of the Institute).

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Translated by J. Salák.